Evaluation of the Force-Frequency Relationship as a Descriptor of the Inotropic State of Canine Left Ventricular Myocardium

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SUMMARY The short-term force-frequency characteristics of canine left ventricular myocardium were examined in both isolated and intact preparations by briefly perturbing the frequency of contraction with early extrasystoles. The maximum rate of rise of isometric tension \( (F'_{\text{max}}) \) of the isolated trabeculae carneae was potentiated by the introduction of extrasystoles. The ratio of \( F'_{\text{max}} \) of potentiated to control beats (force-frequency ratio) was not altered significantly by a change in muscle length. However, exposure of the trabeculae to isoproterenol \( (10^{-7} \text{ M}) \) significantly changed the force-frequency ratio obtained in response to a constant frequency perturbation. Similar experiments were performed on chronically instrumented conscious dogs. Left ventricular minor axis diameter was measured with implanted pulse-transit ultrasonic dimension transducers, and intracavitary pressure was measured with a high fidelity micromanometer. Atrial pacing was performed so that the end-diastolic diameters of the beats preceding and following the extrasystole could be made identical. Large increases in the maximum rate of rise of pressure \( (P'_{\text{max}}) \) were seen in the contraction after the extrasystole. The ratio of \( P'_{\text{max}} \) of the potentiated beat to that of the control beat was not changed by a 9% increase in the end-diastolic diameter, produced by saline infusion. Conversely, isoproterenol significantly altered this relationship in the same manner as in the isolated muscle. Thus, either in vitro or in situ, left ventricular myocardium exhibits large functional changes in response to brief perturbations in rate. The isoproterenol and length data indicate that the force-frequency ratio reflects frequency-dependent changes in the inotropic state, independent of changes in length.

THE SEARCH for an "index of cardiac contractility," that is to say, a quantity sensitive to a change in myocardial inotropism but not to a change in myocardial loading, has yielded a variety of parameters and derived indices that are affected by inotropic interventions. Unfortunately, each of these parameters has been found to be dependent either on muscle length or systolic loading.\(^3\)\(^7\) Recently, however, an index based on the rate-dependency of myocardial performance (exemplified by post-extrasystolic potentiation) has been found to satisfy the criteria for such an index of contractility in isolated right ventricular papillary muscles. The relationship was independent of muscle length yet sensitive to the effects of inotropic interventions.\(^8\)

Many investigators have observed frequency-dependent changes in myocardial function. However, it currently is controversial as to whether the force-frequency properties of isolated, nonperfused myocardium are similar in magnitude to those of the heart in the intact animal. Kavaler et al.\(^9\) found that although large, steady state, frequency-dependent changes in contractile force occurred in isolated myocardium, such changes were essentially absent in papillary muscle experiments in situ. The results of these studies in vivo, however, could have been influenced by the effects of general anesthesia and cardiopulmonary bypass. Higgins et al.\(^10\) observed significant alterations in left ventricular performance after a change in heart rate in anesthetized dogs, but found, as did Noble et al.,\(^11\) that...
these effects were minimal in the conscious dog. These findings were primarily describing steady state conditions late after a change in the frequency of contraction.

However, Kavalier and Noble demonstrated in these same studies that the changes in contractile force early after an alteration in frequency or following an extrasystole could be quite prominent in myocardium in situ. The studies described in this paper were designed to examine such early frequency-dependent changes in function in isolated canine left ventricular myocardium and also in the intact left ventricle of the conscious dog. Experiments were performed to evaluate the effects of pharmacological alterations in the inotropic state and changes in muscle length on this component of the force-frequency relationship in both preparations.

Methods

**ISOLATED MUSCLE EXPERIMENTS**

**Preparation**

Six mongrel dogs weighing 9-10 kg were anesthetized with sodium pentobarbital (25 mg/kg, iv). Each heart was removed within 2 minutes after administration of the pentobarbital and 30 seconds after a left thoracotomy and placed into Krebs-Henseleit solution aerated with a gas mixture of 95% O₂ and 5% CO₂ at 38°C. A trabecula carneae was excised from the left ventricle and mounted in an isometrically in a tissue bath. Each end of the trabecula was pierced with a stainless steel hook; one hook was attached to a semiconductor strain gauge force transducer (resonant frequency = 250 Hz, compliance = 10⁻⁶ cm/dyne) and the other hook was attached to a silver post at the opposite end of the bath. The force transducer was mounted on a worm screw with a vernier so that the muscle length could be controlled and measured. The muscles were studied at a length at which the maximum rate of rise of force was maximal. The bath, its temperature control system, and the pacing device have been described elsewhere. The two strain gauges of the transducer formed two arms of a Wheatstone bridge while a Tektronix carrier preamplifier (type 3C 66) provided the other two arms. The force signal was filtered by a Tektronix differential amplifier (AM 402 DC) with the high frequency filter set at 300 Hz. The data were digitally sampled at a rate of 1 kHz and processed by a PDP 12 digital computer. A signal indicating the occurrence and timing of the test stimulus relative to the regular stimuli and a logic signal indicating the corresponding section of the force signal to be analyzed were digitized simultaneously. The force signal was monitored simultaneously on an oscilloscope, and when fused or otherwise unacceptable contractions were noted the data were eliminated from the subsequent analysis. The digital numerical data were smoothed (least squares polynomial fit of each five consecutive samples) and referenced to the voltage at the moment of stimulation. The maximum rate of rise of force during a contraction was obtained by detecting, on the second execution of the least squares procedure, the linear fit with the fastest slope. The peak muscle force and the maximum rate of rise of force for the contractions of interest then were printed out together with the time between the last regular stimulus and these values.

**Experimental Procedure**

The two-stage experiment described by Johnson et al. was used in these studies. This method is based on the concept that the force-frequency relationship can be divided into two components: an initial, rapidly equilibrating component and a subsequent slowly equilibrating component. During the rapid phase or the first few beats after a frequency alteration, large changes in the force of contraction may be observed. Thereafter, during the slow phase, the beat-to-beat changes that can be demonstrated are much smaller until a new steady state is achieved. In the present paper, only the short-term or rapidly equilibrating effects of a change in the rate of stimulation were evaluated. The experimental procedure was in two stages: the first described the time course of recovery of the maximum rate of rise of force after a regular contraction; the second described how this time course was altered by the introduction of an extrasystole. The extrasystole, in essence, induced a brief, transient perturbation of the basic frequency of contraction.

In the first stage of the experiment, the muscle was paced at a constant frequency of 20/min. A single test stimulus was interpolated into the pacing sequence after every seventh regular contraction. The maximum force derivative (Fₘₐₙₜ) developed during the test contraction was plotted as a function of the time interval between the test stimulus and the preceding regular stimulus (Fig. 1). The test stimulus was introduced infrequently (between every seventh and eighth regular stimulus) so that Fₘₚₓ of the last regular contraction would return to the same control value regardless of the timing of the previous test stimulus. In the second stage of the experiment an early extrasystole was positioned at a fixed interval (225 msec) after every seventh regular contraction, and a test stimulus was introduced at various intervals after this fixed extrasystole. Fₘₚₓ of the test contractions was plotted as a function of the interval between the test stimulus and the preceding regular stimulus (Fig. 1). Since, in the second stage, two stimuli were interpolated (compared to a single stimulus in the first stage), the average overall rate of stimulation would differ in the two stages. To eliminate this difference, a superfluous extra stimulus was introduced after the test stimulus in the first stage of the experiment to ensure that the overall rate of contraction in both stages was identical.

An abridged version of the two-part experiment was used to describe the changes in the force-frequency relationship that occur following a change in the length of the muscle. As in the second stage of the above experiment, the basic rate was kept constant, and an early extrasystole was introduced at a fixed interval (225 msec) following every seventh regular contraction. A test stimulus was introduced after each fixed extrasystole, but the interval preceding the test stimulus was maintained constant throughout the experiments (2.5 seconds). This test stimu-
Animal Preparation and Instrumentation

Six mongrel dogs (22–31 kg) underwent sterile left thoracotomies through the 5th intercostal space for implantation of dimension transducers on the heart. Ventilation was maintained during the surgical procedure with a Bennett MA1 respirator connected to a cuffed endotracheal tube. Pulse-transit ultrasonic dimension transducers (resonant frequency = MHz) (Transducer Products, LTZ-5) were implanted on the epicardial surface of the left ventricular anterior and posterior walls in order to measure transverse diameter of the minor axis. Bipolar pacing electrodes were sutured to the right atrial appendage, and the thoracotomy was repaired. The connectors from the dimension transducers and the pacing wires were left in a subcutaneous pouch just below the left shoulder. The dogs received intramuscular injections of procaine penicillin G (6 x 10^6 U) and dihydrostreptomycin (0.5 g) for 5 days after surgery.

Six to 32 days postoperatively, each dog was studied in the conscious state. Because of thorough training, local 1% lidocaine (Xylocaine) anesthesia without sedation suffered during exteriorization of the implanted connectors and pacing wires. A Millar PC350 micromanometer was introduced percutaneously into the right femoral artery and passed retrograde into the left ventricle using fluoroscopic guidance. The micromanometer (resonant frequency = 25–35 kHz) was balanced and statically calibrated with a column of 38°C water. The measured zero baseline drift of this manometer during use in vivo was less than 0.5 mm Hg in every study. The pressure signal was processed by a model 8805C Hewlett-Packard carrier preamplifier with a high frequency filter set at 240 Hz.

The connectors from the dimension transducers were directly coupled to a sonomicrometer. With 5-MHz transducers the minimum resolution of this system was approximately 0.05 mm, and the crystal separation to voltage output relationship was linear over the ranges encountered in this study. The electronic drift of the sonomicrometer was less than 0.05 mm/hour; the signals were calibrated by substituting an electronically generated time delay into the circuitry. The use of sonomicrometry to measure cardiac dimensions has been presented in detail elsewhere.14 These studies demonstrated the validity of using epicardial minor axis diameter measurements to describe changes in ventricular volume.

The pressure and dimension waveforms and lead I of the electrocardiogram were recorded on analog tape at 3/4 inches/sec with a model 3520B Hewlett-Packard 8 channel FM recorder. At the time of data analysis, left ventricular pressure was differentiated using a model 8818A Hewlett-Packard derivative computer with the high frequency filter set at 100 Hz. The differentiator was calibrated by a ramp wave produced by a Wavetek wave function generator. Data measurement was performed with a model 7700 Hewlett-Packard thermal penwriter at a paper speed of 100 mm/sec. The frequency response of the penwriter was flat to 70 Hz, and a sinusoidal test signal was diminished in amplitude by 15% at a frequency of 100 Hz.

Experimental Procedure

As in the isolated muscle experiments, analysis of the force-frequency relationship in the intact left ventricle was accomplished with a two-stage experiment. Only dogs with intrinsic heart rates of less than 90/min were accepted for

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**Figure 1** A schematic representation of the two-stage experiment. The constant basic interval is labeled R. In the top diagram the first stage of the experiment is depicted. A test stimulus (T) is interpolated at various test stimulus intervals (TSI), in the isolated preparation, after every seventh stimulus at the basic rate. To ensure that the muscle rates in the first and second stage are the same, a supernuous stimulus (S) is introduced. In the second stage of the experiment, (bottom diagram) an extra stimulus (E) is interpolated at a fixed extra stimulus interval (ESI), in the isolated preparation, after every seventh stimulus at the basic rate, and a test stimulus (T) is then introduced after the extra stimulus at various test stimulus intervals (TSI) after the last regular stimulus.

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The data prior to and following a length change or exposure to isoproterenol were compared by paired t-test.
study. Pacing was performed via the implanted right atrial electrodes at 10% above threshold with a Devices 2533 isolated stimulator triggered by a specially designed digital pulse generator. In both parts of the experiment the regular interval was controlled at 600 msec (frequency = 100/min). Following every 12th regular stimulus the basic rate was suspended for 1 second. In the first stage of the experiment a single test stimulus was introduced at varying intervals during this pause, and the maximum left ventricular pressure derivative (Pmax) of the test contraction was plotted as a function of the time interval between the test systole and the preceding regular systole (Fig. 1). In the second stage of the experiment, an early extrasystole was introduced at a fixed interval of 250 msec (frequency = 240/min) during the pause following every 12th regular beat, and a test stimulus was introduced at various intervals after the fixed extrasystole. Thus, the early extrasystole produced a transient perturbation in the frequency of contraction from 100/min to 240/min. Pmax of the test contraction was plotted as a function of the interval between the test systole and the preceding regular systole. The end-diastolic diameter of each contraction was determined from the dimension trace.

To evaluate the effects of a change in ventricular diameter on the force-frequency relationship, the abridged experiment was performed. The heart was paced at a constant frequency, and a fixed extrasystole was introduced after every 12th regular beat. A single test stimulus was introduced after the extrasystole at the interval which allowed the end-diastolic diameter to return to that of the previous contraction. The ratio of Pmax of the test contraction to Pmax of the last regular contraction was determined.

During this pacing sequence, isotonic sodium chloride solution was rapidly infused into a peripheral vein at a rate of at least 100 ml/min. The force-frequency ratio was determined as the end-diastolic diameter increased, utilizing only sequences in which the end-diastolic diameters of the regular and test contractions were identical. In all of the dogs a tachycardia ultimately occurred during the infusion (Bainbridge reflex). However, in four dogs at least a 9% increase in the measured transverse end-diastolic diameter was produced before reflex changes interfered with the ability to pace the dogs. In these four dogs five sequential force-frequency ratios obtained in the control state were compared to five ratios obtained after the maximum diameter change, using a paired t-test.

To evaluate the effects of an inotropic intervention, isoproterenol (2 × 10^-5 M solution) was continuously infused at 0.191 ml/min into a peripheral vein in five dogs. An abridged experiment was performed as previously described. The basic stimulation frequency during a steady state response to isoproterenol was set about 10% greater (120-150/min) than the spontaneous heart rate. The first extrasystole was introduced at a fixed interval (e.g., 300 msec), and the subsequent test stimulus was introduced at an interval which allowed the end-diastolic diameter to return to control. The force-frequency ratio obtained during isoproterenol infusion was compared to that measured using an identical pacing sequence in the control state. Data during each intervention were compared to data obtained in the control state, using a paired t-test.

**Results**

**ISOLATED MUSCLE EXPERIMENTS**

Figure 2 illustrates representative data obtained with the two-stage experiment described diagrammatically in Figure 1. In the first stage of the experiment, Fmax of the test contraction that followed the regular contraction was small when the preceding interval was short, and, as the test stimulus interval was increased, Fmax of the test contraction increased progressively. As the test stimulus interval approached the regular interval, Fmax of the test contraction approached that of the regular contraction. In the second stage of the experiment, Fmax of the test contractions was again small at short test intervals. However, as compared to the first stage of the experiment, Fmax increased to a much higher plateau value as the test stimulus interval was lengthened. When the Fmax values on the plateau portions of the two curves (test stimulus intervals of 2.5 seconds) were compared for the six left ventricular trabeculae, the mean ratio of Fmax of the second stage plateau to Fmax of the first stage plateau was 1.95 ± 0.09 SEM.

**Effects of Changes in Length**

To describe the time course of the effects of trabecular length on the force-frequency relationship, the abridged version of the two-part experiment was utilized; the response of the muscle following a change in length can be divided into two components. In the initial component the force-frequency ratio declined regardless of the direction of the length change and then returned to its original value within 1-20 minutes. In the second component the ratio...
remained constant although $F_{\text{max}}$ continued to change gradually until a new stable value of $F_{\text{max}}$ was reached. The nature of the initial transient is unknown but may be related to catecholamine release, as the magnitude and duration of the transient can be markedly reduced with propranolol. Neglecting the initial transient component, the steady state force-frequency ratio was constant over the range of lengths examined in this study (Fig. 3). Thus, a change in length proportionally increased the control and potentiated values of $F_{\text{max}}$ obtained in response to a transient alteration in the frequency of contraction.

Effects of Isoproterenol

The effects of isoproterenol on the force-frequency relationship are illustrated in Figure 4. $F_{\text{max}}$ of all contractions was potentiated by isoproterenol. With the increasing force of contraction, not only were the plateau values of the first and second stages of the experiment brought together, but there was a change in the qualitative characteristics of the second curve. $F_{\text{max}}$ did not monophasically increase to a plateau value as the test interval increased, but, instead, rose initially and then fell. The alteration in the short-term force-frequency relationship by isoproterenol can also be shown with the abridged experiment (Fig. 4). The $F_{\text{max}}$ values of the regular and the test contractions were both increased during infusion with isoproterenol, but the increase in strength of the regular contraction was relatively larger than that of the test contraction. As a result, the force-frequency ratio was diminished from 1.96 ± 0.09 SEM to 1.41 ± 0.03 SEM ($P < 0.03$). Exposure of the muscle to isoproterenol thus decreased the ratio by 27 ± 4% (SEM) in the trabeculae studied.

EXPERIMENTS ON INTACT DOGS

The analog measurements obtained from a representative study are shown in Figure 5. The changes in $P_{\text{max}}$ that were observed in the conscious dog with the use of the two-stage experiment are illustrated in Figure 6. In all dogs studied, $P_{\text{max}}$ of the test contractions in the first stage of the experiment rose from a small value to that of the previous regular systole as the test stimulus interval approached that of the basic pacing interval. In the second stage of the experiment, $P_{\text{max}}$ of the test contractions also rose as the test stimulus interval was increased but to a plateau value that exceeded that of the first stage. The end-diastolic diameter of the test contractions varied throughout the experiment, since ventricular volume was lower at the earlier test stimulus intervals. Therefore, the entire curves could not be quantitatively compared with those of the isolated trabeculae where the muscle was contracting at a constant length. However, the plateau portions of the curves illustrated in Figure 6 could be.
compared over the range where the end-diastolic diameters of the test contractions were equivalent to control. The ratio of $P_{\text{max}}$ of the test beat at the isovolumic portion of the curve to $P_{\text{max}}$ of the previous regular beat, which is the same as the first-stage plateau value, was determined. At a fixed frequency perturbation (i.e., basic frequency = 100/min, early extrasystole frequency = 240/min) the mean force-frequency ratio in six dogs was 1.65 ± 0.09 SEM.

Effects of Changes in End-Diastolic Minor Axis Diameter

The abridged experiment (Fig. 5) was used to determine the force-frequency ratio at a control diameter and during the infusion of isotonic saline. As the left ventricular diameter increased, $P_{\text{max}}$ values for the regular contraction and the test contraction increased (Fig. 7). Only data obtained before changes in the intrinsic heart rate interfered with the ability to control the dog's heart rate were utilized. The values of $P_{\text{max}}$ for the test and regular beats were increased proportionally as the end-diastolic diameter increased during infusion so that the force-frequency ratio was not altered throughout the infusion. In all four dogs the ratios obtained in the control state were not significantly different from those obtained after the maximum dimension change ($P > 0.5$). Again, all comparisons were made using data acquired before the reflex tachycardia.

Effects of Isoproterenol

The abridged experiment was carried out prior to and during the infusion of isoproterenol. In every dog studied the values of $P_{\text{max}}$ of the regular and test contractions increased in response to isoproterenol. However, the effects of this intervention on the regular and test contractions were not proportional, in that $P_{\text{max}}$ of the regular beat was increased to a greater degree. As a result, the force-frequency ratio was diminished significantly in every dog by the infusion of isoproterenol (Fig. 8).

Discussion

Until recently, studies in the intact animal have not supported the hypothesis that frequency-dependent changes in myocardial function determine to any significant degree the performance of the heart in the conscious animal. Although previous studies have emphasized the minimal dependency of myocardial performance on the steady state heart rate, Mahler et al.18 recently have shown that left ventricular function in the conscious dog is significantly affected, at least in the short term, by frequency-
The effects of isoproterenol on the force-frequency relationship in five dogs. The ratio of $P_{\text{mai}}$ for the test systole to $P_{\text{max}}$ of the regular systole in the control state (C) and during isoproterenol infusion (I) are connected by lines. Each dog was evaluated with a different rate perturbation. The $P$ value was less than 0.01 for every study. The vertical bars illustrate the standard error of the mean.

A previous evaluation of how the short-term, rapid phase of the force-frequency relationship is affected by muscle length has demonstrated that the effects of a variation in the rate and pattern of stimulation and those of length interact in a multiplicative fashion:

$$F_{\text{max}} \propto \phi \cdot \lambda$$

(1)

where $F_{\text{max}}$ describes myocardial performance, $\phi$ is the inotropic function affected by the frequency of contraction, and $\lambda$ is the length-dependent function. This interrelationship, which is a manifestation of the Frank-Starling relationship, was obtained in isolated myocardium only when the maximum isometric force derivative was used as a measure of muscle function. In the present study, the force-frequency ratio, measured at a given frequency alteration, was independent of trabecular length, i.e., the control and potentiated values of $F_{\text{max}}$ were increased proportionally by a change in length (Fig. 3). Therefore, Equation 1 appears to be a valid description of the interaction of the frequency-dependent, inotropic function ($\phi$) and the length function ($\lambda$) in isolated left ventricular myocardium.

This analysis is based on the assumption of isometric contraction of the muscle, a condition which is not present in the intact heart. However, because isovolumic contraction is fairly isometric in the resting, conscious dog, this assumption is approximated when an isovolumic parameter such as $P_{\text{mai}}$ is used to describe left ventricular function. Furthermore, $F_{\text{max}}$ should be independent of the load resisting systole shortening since $P_{\text{mai}}$ occurs before aortic valve opening in the conscious dog. This assumption is supported by the data of Van den Bos et al. which show that sudden large increases in diastolic aortic pressure have no statistically significant effect on $F_{\text{max}}$ of the subsequent contraction in the conscious dog. An equation similar to Equation 1 then may be theoretically formulated for the intact left ventricle:

$$P_{\text{max}} \cdot G \propto \phi \cdot \lambda$$

(2)

where $G$ is the geometric factor which relates $P_{\text{max}}$ to $F_{\text{max}}$ within the left ventricular wall. If the end-diastolic geometry of both the previous regular and the test beat is identical, then $G$ and $\lambda$ for these two beats are likewise identical. Thus, a ratio of the isolength values of $P_{\text{mai}}$ of the test and previous regular beat should reflect only a change in the $\phi$ function, and the effects of ventricular geometry on the observed potentiation would be nullified. Therefore, the force-frequency ratio, as measured in the present study, should reflect only the change in the inotropic state that is produced by the frequency perturbation, independent of muscle length. This hypothesis was tested by the saline infusion experiments and appears to be valid over the geometric ranges evaluated. Thus, using the technique described in this paper, the frequency-dependent changes in the inotropic state can be determined in the intact heart independent of ventricular geometry.

In contrast, the force-frequency ratio was significantly altered by a pharmacological inotropic intervention. Isoproterenol diminished the ratio both in the isolated trabec-
ulation and in the intact left ventricle. Although this ratio is sensitive to a change in myocardial inotropism, it should be emphasized that the ratio is not an index of the absolute level of the inotropic state but rather reflects the frequency-dependent inotropic reserves of the myocardium. However, if these inotropic reserves are changed in a consistent and recognizable way by myocardial failure, the technique presented in this paper might be of value in analyzing directional changes in myocardial function induced by heart failure and elucidating the underlying mechanisms producing them.

In the present study, the method used to test the length-dependence of the force-frequency relationship in the conscious dog has several inherent limitations. It is impossible to change the end-diastolic geometry of the left ventricle without inducing a certain degree of reflex autonomic activity in the intact animal. This point is illustrated by the fact that a reflex tachycardia was ultimately observed in every dog during infusion. However, the length changes illustrated in Figure 7 are probably as pure as can be produced in the intact heart, since no detectable change in the ability to totally control the dog’s heart rate was observed at the time of data collection. Several investigators have shown that volume loading does not enhance the steady state value of $P_{\text{max}}$ to a significant degree in the conscious animal.\(^6\)\(^7\) However, if data were obtained during the initial phases of infusion, prior to the onset of reflex changes, there does appear to be an initial increase in $P_{\text{max}}$ with volume loading, consistent with the Frank-Starling relationship.\(^7\)

Although it appears that the force-frequency relationship is altered by inotropic interventions and is independent of muscle length, several important questions were not answered by the present study. To be of practical value, the ratio would have to be fairly constant from day to day in the same subject. The normal variability in the ratio from subject to subject should also be defined. Investigation of how the functional response to a frequency perturbation is altered by stable hypertrophy or myocardial failure seems indicated. Thus, further studies will be necessary to define the exact role of the force-frequency relationship in the evaluation of left ventricular function.

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